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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/186,475	11/04/1998	ANNIE FONG	238/046	1830
7590 Stephen D. Prodnuk, Esq. Pfizer, Inc. Pfizer La Jolla Labs 10777 Science Center Drive San Diego, CA 92121		03/09/2007	EXAMINER CANELLA, KAREN A	
			ART UNIT 1643	PAPER NUMBER
SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
3 MONTHS		03/09/2007	PAPER	

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No. 09/186,475	Applicant(s) FONG ET AL.	
	Examiner Karen A. Canella	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3, 6, 8-11, 16, 18-20, 23, 27, 28, 31 and 32 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-3, 6, 8-11, 16, 18-20, 23, 27, 28, 31 and 32 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>May 3, 1999</u> . | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

Claims 1-3, 6, 8-11, 16, 18-20, 23, 27, 28, 31 and 32 are pending. The Election of Species Requirement of May 24, 2001 and the finality of the Office action of May 18, 2004 is hereby withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 23, 27 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "said marker is vascular endothelial growth factor mRNA" in claim 27 lacks antecedent basis in claims 1 which is limited to markers selected from tissue actor, CD40, uPA, ETS-1, Il-8 and t-PA.

It is unclear how claim 31 further limits the scope of claim 1. Claim 1 requires the determination of an efficacious dose. Claim 31 states that said dose is between a minimal and a maximal dose. An efficacious dose of any kind will always have a less than optimum dose and a greater than optimum dose. Thus claim 31 does not alter the metes and bound of the efficacious dose of claim 1.

The metes and bound of claim 23 is unclear. claim 23 is dependent on claim 1 which requires that a determination be made of an efficacious dose to be administered to a subject. however, the compound is administered to the patient, and thus the samples would be reasonably construed to have been taken from the patient versus the subject.

Claims 1-3, 6, 8-11, 16, 18-20, 23, 27, 28, 31 and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods requiring monitoring the release of a secreted protein marker, does not reasonably provide enablement for methods for monitoring the release of a polynucleotide or of monitoring the release of the markers of tissue actor, CD40, uPA, Il-8 and t-PA. in samples which include saliva, cells isolated from saliva, spinal fluid, amniotic fluids. The specification does not enable any person skilled in the art to

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which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 1 specifies an active method step for monitoring the release of a marker selected from tissue actor, CD40, uPA, ETS-1, IL-8 and t-PA. All of the recited species are protein in nature and are released in response to a compound incorporating the structure of Formula I. ETS-1 is a transcription factor and not normally released by a viable intact cell. further claims 16, 20, 27 and 28 require the monitoring of a marker which is a polynucleotide and nor normally released by the cell. It would be undue experimentation for one of skill in the art to measure release of the recited polynucleotides using plasma, serum, urine saliva, in response to the administered compounds.

Claims 10 encompasses a sample selected from a blood fraction, saliva, cells isolated from saliva, spinal fluid, amniotic fluid. The specification teaches that tissue plasminogen activator is predominantly release from endothelial cells. (page 25, lines 9-14) The specification teaches that CD40 is distributed on tumor capillaries (page 24, lines 16-20). the specification teaches that uPA and uPAR are associated with the invasive phenotype of endothelial cells in renal cell carcinoma (page 24, lines 21-26). The specification teaches that VEGF is a hormone which induce angiogenesis . One of skill in the art would reasonably conclude that the markers of TF, CD40, uPA, IL-8 and tPA can be found in the blood and in the urine. However, the claims encompass biological samples which are not related to blood or serum. The specification provides no objective evidence that samples of fluids from other body compartments such as spinal fluid, amniotic fluid, urine (with the exception of uPA), and cells isolated from saliva, would comprise levels of the TF, CD40, uPA, IL-8 or tPA which would be useful for the determination of an efficacious dose of the compounds of formula I. One of skill in the art would be required to establish first that TF, CD40, uPA, IL-8 or tPA markers can pass through, or be carried to, other body fluid compartments without degradation, and be present at levels which are useful for the establishment of an effective dose of a compound in fluids such as urine and saliva. It is noted that claim 10 also encompasses a urine fraction, but no guidance is given in the specification for the required parameters of said fraction. Thus, one of skill in the art would not have a reasonable expectation of success in practicing the claims invention using the broadly claimed biological samples. It is further noted that claim 10 encompasses a "biopsy of

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endothelial cells". Claim 1 requires determining the amount of marker released per known number of cells as a function of the dose of the compound of formula I. A biopsy would contain an unknown number of tumor cells mixed in with an unknown number of stromal cells and invading immune cells. One of skill in the art would be forced into undue experimentation in order to carry out the method of claim 1 using a biopsy of endothelial cells as a sample.

1. The rejection of claims 1-3, 9-11, 16, 18, 23, 28, 31 and 32 under 35 U.S.C. 103(a) as being obvious over Tang et al (US 5,880,141) in view of Foulkes et al (US 5,580,722) is maintained for reasons of record. Amended claims 6, 8 are also rejected for the same reasons of record.

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Claim 1 is drawn to a method of determining an efficacious dose of a compound administered to a subject for the purpose of modulating angiogenesis comprising the steps of (a) administering the compound to a patient wherein the compound is a receptor antagonist that inhibits a receptor involved in angiogenesis, (b) monitoring a marker selected from the group consisting of tissue factor, CD40, u-PA, ETS-1, IL8 and t-PA, (c) constructing a standard curve

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and (d) determining the efficacious dose based on the standard curve. claim 1 is examined to the extent that it reads on compound A. claim 2 embodies the method of claim 1 wherein conditions associated with angiogenesis include cell proliferation. Claim 3 embodies the method of claim 3 wherein the conditions associated with cell proliferation are cancer, arthritis, and endometriosis and ocular neovascularization. Claim 9 embodies the method of claim 1 wherein the marker is present in a sample obtained from said subject. Claim 10 is examined to the extent that it reads on whole blood and fractions thereof. Claim 11 embodies the method of claim 10 wherein the sample comprises monocytes. Claim 16 is examined to the extent that it reads on the detection of a protein marker. claim 17 embodies the method of claim 1 wherein the step of monitoring a marker comprises the step of determining the presence or amount of said marker. Claim 18 embodies the method of claim 17 wherein the presence or amount of said marker is detected by an antibody. Claim 23 embodies the method of claims 16-18 wherein said marker is present in a sample collected from a subject. Claim 23 is examined to the extent that it reads on whole blood or fractions thereof which are collected from a subject. Claim 24 embodies the method of claim 1 wherein the step of monitoring a marker related to angiogenesis comprises the step of comparing said marker to a standard. Claim 28 is drawn to the method of claim 1 and is examined to the extent that it reads on detecting the marker with antibodies, enzyme-linked immunosorbent assay, solid phase enzyme immunoassay with polyclonal antisera. Claim 29 embodies the method of claim 1 wherein said efficacious dose is where additional amounts of drug cause a downward slope of greater than 5% in said standard. Claim 30 is drawn to the method of claim 1 wherein additional amounts of the drug causes a change of less than 5% in the slope of said standard. Claim 31 embodies the method of claim 1 wherein said efficacious dose is between minimal and maximal dose. claim 32 embodies the method of claim 1 wherein said marker is tissue factor.

Tang et al teach a method for screening for compounds having protein tyrosine kinase inhibitory activity by means of in vivo experiments (column 7, lines 47-54). Tang et al teach that compound A is a compound which is capable of regulating and or inhibiting tyrosine kinase signal transduction (column 3, lines 35-67). Note that column 3, line 58 indicates that X is "O", and R1 is a 5 membered heteroaryl, substitutes with C-alkyl, and that R2-R5 is hydrogen. Tang et al teach that the disclosed tyrosine kinase inhibitors are intended for use in methods for

treating diseases comprising proliferation or metabolic disorders, for example cancer, fibrosis, psoriasis, atherosclerosis, arthritis, and other disorders related to abnormal vasculogenesis and/or angiogenesis, such as diabetic retinopathy (column 4, lines 32-37) and that tyrosine kinase signal transduction controls cell proliferation and differentiation and that abnormal cell proliferation may result in a wide array of disorders and diseases, including the development of neoplasia such as carcinoma, sarcoma, leukemia, glioblastoma, hemangioma, psoriasis, arteriosclerosis, arthritis and diabetic retinopathy (or other disorders related to uncontrolled angiogenesis and/or vasculogenesis) (column 6, lines 22-29). Tang et al teach that the determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided (column 12, lines 50-53) and that the therapeutically effective dose can be estimated initially from cell culture assays followed by a preclinical assay wherein a dose can be formulated in an animal model to achieve a circulating concentration range that includes the IC₅₀ as determined in cell culture (i.e., the concentration of the test compound which achieves a half-maximal inhibition of the PTK activity) and that such information can be used to more accurately determine useful doses in humans. Tang et al teach that a therapeutically effective dose refers to that amount of the compound that results in amelioration of symptoms or a prolongation of survival in a patient and that toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD₅₀ and ED₅₀. Compounds which exhibit high therapeutic indices are preferred. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition (column 12, line 63-column 13, line 16). Tang et al also teach that dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the kinase modulating effects,

or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from in vitro data; e.g. the concentration necessary to achieve 50-90% inhibition of the kinase using the assays described herein. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration and that bioassays can be used to determine plasma concentrations (column 13, lines 17-27). Tang et al do not specifically recite the limitation of determining a standard curve and determining the efficacious dose based on said standard curve, although the limitations appear to be inherent within the method disclosed by Tang et al. Tang et al teach the monitoring of receptor tyrosine kinase activity in cell lines by means of antibody-based detection systems (beginning in column 14, within section 6, entitled "RTK assays"). Tang et al do not teach the method wherein whole blood or fractions thereof are monitored by detecting the presence or amount of t-PA, u-PA or tissue factor.

It is noted that Tang et al teach that uncontrolled cellular proliferation can lead to atherosclerosis and vasculogenesis. Foulkes et al teach a method for modulating genes that encode a protein of interest associated with the treatment of atherosclerosis or restinosis (abstract). Foulkes et al teach that monocyte attach to the endothelium and enter into the arterial wall (column 2, lines 3-6). Foulkes et al teach that atherosclerotic plaques develop into thrombogenic plaques (column 6, lines 21-34) and that t-PA, u-PA and tissue factor as proteins which are associated with thrombosis (column 21, lines 55-67). Foulkes et al specifically teach that the plasminogen activators such as t-PA are anti-thrombogenic and plasminogen activator inhibitor is associated with thrombosis (column 6, lines 15-20).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to determine an efficacious dose for the purpose of modulating angiogenesis, comprising administering to a subject compound A, monitoring a marker in the blood or a fraction thereof taken from said patient, wherein the marker is selected from the group consisting of tissue factor, u-PA and t-PA. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Foulkes et al on u-PA, t-PA and tissue factor as proteins of interest with respect to the condition of thrombosis, and the correlation between thrombosis and atherosclerosis restinosis; and the teachings of Tang et al on methods of determining an efficacious dose of protein kinase inhibitor, and the association between cell proliferation, angiogenesis, and atherosclerosis.

2. The rejections of claims 1-3, 9-11, 16, 18, 23, 28, 31 and 32 under 35 U.S.C. 103(a) as being obvious over Tang et al (US 5,880,141) in view of the abstract of Peirce et al (Glycoconjugate Journal, 1997, Vol. 14, pp. 623-630) and Galan et al (Journal of Biological chemistry, 1996, Vol. 271, pp. 7992-7998) is maintained for reasons of record. Amended claims 6 and 8 are also rejected for the same reasons of record.

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Claim 1 is drawn to a method of determining an efficacious dose of a compound administered to a subject for the purpose of modulating angiogenesis comprising the steps of (a) administering the compound to a patient wherein the compound is a receptor antagonist that inhibits a receptor involved in angiogenesis, (b) monitoring a marker selected from the group consisting of tissue factor, CD40, u-PA, ETS-1, IL8 and t-PA, (c) constructing a standard curve and (d) determining the efficacious dose based on the standard curve. claim 1 is examined to the extent that it reads on compound A. claim 2 embodies the method of claim 1 wherein conditions associated with angiogenesis include cell proliferation. Claim 3 embodies the method of claim 3 wherein the conditions associated with cell proliferation are cancer, arthritis, and

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endometriosis and ocular neovascularization. Claim 9 embodies the method of claim 1 wherein the marker is present in a sample obtained from said subject. Claim 10 is examined to the extent that it reads on whole blood and fractions thereof. Claim 11 embodies the method of claim 10 wherein the sample comprises monocytes. Claim 16 is examined to the extent that it reads on the detection of a protein marker. Claim 17 embodies the method of claim 1 wherein the step of monitoring a marker comprises the step of determining the presence or amount of said marker. Claim 18 embodies the method of claim 17 wherein the presence or amount of said marker is detected by an antibody. Claim 23 embodies the method of claims 16-18 wherein said marker is present in a sample collected from a subject. Claim 23 is examined to the extent that it reads on whole blood or fractions thereof which are collected from a subject. Claim 24 embodies the method of claim 1 wherein the step of monitoring a marker related to angiogenesis comprises the step of comparing said marker to a standard. Claim 28 is drawn to the method of claim 1 and is examined to the extent that it reads on detecting the marker with antibodies, enzyme-linked immunosorbent assay, solid phase enzyme immunoassay with polyclonal antisera. Claim 29 embodies the method of claim 1 wherein said efficacious dose is where additional amounts of drug cause a downward slope of greater than 5% in said standard. Claim 30 is drawn to the method of claim 1 wherein additional amounts of the drug causes a change of less than 5% in the slope of said standard. Claim 31 embodies the method of claim 1 wherein said efficacious dose is between minimal and maximal dose. Claim 32 embodies the method of claim 1 wherein said marker is tissue factor.

Tang et al teach a method for screening for compounds having protein tyrosine kinase inhibitory activity by means of in vivo experiments (column 7, lines 47-54). Tang et al teach that compound A is a compound which is capable of regulating and or inhibiting tyrosine kinase signal transduction (column 3, lines 35-67). Note that column 3, line 58 indicates that X is "O", and R1 is a 5 membered heteroaryl, substitutes with C-alkyl, and that R2-R5 is hydrogen. Tang et al teach that the disclosed tyrosine kinase inhibitors are intended for use in methods for treating diseases comprising proliferation or metabolic disorders, for example cancer, fibrosis, psoriasis, atherosclerosis, arthritis, and other disorders related to abnormal vasculogenesis and/or angiogenesis, such as diabetic retinopathy (column 4, lines 32-37) and that tyrosine kinase signal transduction controls cell proliferation and differentiation and that abnormal cell proliferation

may result in a wide array of disorders and diseases, including the development of neoplasia such as carcinoma, sarcoma, leukemia, glioblastoma, hemangioma, psoriasis, arteriosclerosis, arthritis and diabetic retinopathy (or other disorders related to uncontrolled angiogenesis and/or vasculogenesis) (column 6, lines 22-29). Tang et al teach that the determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided (column 12, lines 50-53) and that the therapeutically effective dose can be estimated initially from cell culture assays followed by a preclinical assay wherein a dose can be formulated in an animal model to achieve a circulating concentration range that includes the IC₅₀ as determined in cell culture (i.e., the concentration of the test compound which achieves a half-maximal inhibition of the PTK activity) and that such information can be used to more accurately determine useful doses in humans. Tang et al teach that a therapeutically effective dose refers to that amount of the compound that results in amelioration of symptoms or a prolongation of survival in a patient and that toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD₅₀ and ED₅₀. Compounds which exhibit high therapeutic indices are preferred. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition (column 12, line 63-column 13, line 16). Tang et al also teach that dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the kinase modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from in vitro data; e.g. the concentration necessary to achieve 50-90% inhibition of the kinase using the assays described herein. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration and that bioassays can be used to determine

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plasma concentrations (column 13, lines 17-27). Tang et al do not specifically recite the limitation of determining a standard curve and determining the efficacious dose based on said standard curve, although the limitations appear to be inherent within the method disclosed by Tang et al. Tang et al teach the monitoring of receptor tyrosine kinase activity in cell lines by means of antibody-based detection systems (beginning in column 14, within section 6, entitled “RTK assays”). Tang et al do not teach the method wherein whole blood or fractions thereof are monitored by detecting the presence or amount of ETS-1.

The abstract of Pierce et al teaches that the ETS family of transcriptional activators are upregulated through growth factor receptors that activate tyrosine kinases.

Galang et al teach that ETS is the downstream target of the Neu oncogene and that intervention in the upregulation of ETS may be a useful in therapy for Neu associated cancers (abstract)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to determine an efficacious dose for the purpose of modulating angiogenesis, comprising administering to a subject compound A, monitoring a marker in the blood or a fraction thereof taken from said patient, wherein the marker is ETS-1. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of the abstract of Pierce et al on the activation of ETS by tyrosine kinases and the teachings of Galang et al on the association between ETS activation and cellular transformation and the suggestion of Galang et al that therapeutic intervention in Neu associated cancers be targeted to the downstream targets of Neu which include the ETS transcription factors.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference

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claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 3, 8, 9, 10, 28, and 31, rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3 and 4 of U.S. Patent No. 5,880,141 in view of Takano et al (Cancer Research, 1994, Vol. 54, pp. 2654-2660), or over claims 15-17 and 22-24 of US 5,792,783 in view of Takano et al, or over claims 18 and 19 of US. 5,881,113 in view of Takano et al; or over claims 35-37 of U.S. 5,886,020 in view of Takano et al

The claims of the reference patents encompass methods of treating disease states in which the disease is blood vessel proliferative disease and further wherein the blood vessel proliferative disease is arthritis, comprising administering a compound which fulfills the specific embodiments of formula I. It is noted that arthritis is a limitation of the instant claim 3. the claims of the reference patent do not encompass how to determine the efficacious dose of the compound before it is administered to the subject in need

Takano et al teach that Suramin is an anticancer and angiosuppressive agent that inhibits induction of uPA. Takano et al teach that the release of tPA is monitored by measuring tPA in vitro after exposure of Suramin. Takano et al teach that the mean of uPA activity was determined from a standard curve based on human uPA and the calculation of percent inhibition of induced PA (page 2655, second column, under the heading of "PA induction assay").

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It would have been prima facie obvious to determine the effective dose of Suramin in a subject, comprising administering Suramin to said subject and measuring the percent inhibition of induced uPA , wherein the induction of the optimal anti-angiospressive effect was correlated with the inhibition of uPA. One of skill in the art would have been motivated to do so by the teachings of Takano et al on the nexus between an anticancer effect, and angiosuppressive effect and the inhibition of uPA. One of skill in the art would understand that a Phase II clinical trial is commensurate with establishing the optimal dose of a therapeutic compound.

Applicant has previously argues that the Tang reference was not available as a 103(a) reference because it was commonly owned with the instant application. This is only partially persuasive. The MPEP (718) states

37 CFR 1.130. Affidavit or declaration to disqualify commonly owned patent or published application as prior art.

(a) When any claim of an application or a patent under reexamination is rejected under 35 U.S.C. 103 on a U.S. patent or U.S. patent application publication which is not prior art under 35 U.S.C. 102(b), and the inventions defined by the claims in the application or patent under reexamination and by the claims in the patent or published application are not identical but are not patentably distinct, and the inventions are owned by the same party, the applicant or owner of the patent under reexamination may disqualify the patent or patent application publication as prior art. The patent or patent application publication can be disqualified as prior art by submission of:

- (1) A terminal disclaimer in accordance with § 1.321(c); and*
 - (2) An oath or declaration stating that the application or patent under reexamination and*
- patent or published application are currently owned by the same party, and that the inventor named in the application or patent under reexamination is the prior inventor under 35 U.S.C. 104.*

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In the instant case, a statement separate from the office action which is signed by the appropriate party is required, along with identification of the prior inventor along with a terminal disclaimer is required to disqualify Tang as prior art under 103(a).

All claims are rejected.

All other rejections and objections as set forth or maintained in the previous Office action are withdrawn in light of applicant's arguments.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A. Canella, Ph.D.

2/20/2007



The block contains a handwritten signature in cursive that reads "Karen A. Canella". Below the signature is a circular official stamp. The text in the stamp includes "KAREN A. CANELLA, PH.D.", "Patent Examiner", and "Art Unit 1643". A long, thin arrow is drawn from the right side of the signature, pointing towards the right margin of the page.